

# THE HOPKINS HIV REPORT

A bimonthly newsletter for healthcare providers

## XV International AIDS Conference in Bangkok, Thailand

Complete conference abstracts can be viewed online at <http://www.ias.se/ejias/>

### XV International AIDS Conference in Bangkok: Antiretroviral Therapy

By Joel E. Gallant, M.D., M.P.H.

The XV International AIDS Conference, held in Bangkok, Thailand in July, was a qualified success. The dire predictions of torrential rains, sweltering heat and humidity, and paralyzing traffic jams with 2-hour commutes to and from the conference center all failed to materialize. Memories of the painfully long flights were quickly erased by the welcoming Thai hospitality and superb cuisine. The city and the conference venue were able to handle the over 17,000 attendees without significant glitches. If the scientific and clinical content was at times underwhelming, attendees acknowledged that this conference is increasingly—and appropriately—becoming the most important forum for the discussion of the global AIDS epidemic and the treatment of HIV infection in the developing world. Of course, the content of the conference might have been richer had investigators from NIH and CDC been allowed to attend and present their data. The government's restriction on travel to this conference was roundly criticized, as were its obsession with abstinence programs and its attempts to foster doubts about the effectiveness of condoms. Activist and community groups from all over the world were well represented in Bangkok, with tactics that ranged from responsible and informed advocacy on the one extreme to the liberal use of whistles, megaphones, fake blood and spray-paint on the other. The international AIDS conferences have always been a colorful mix of science, culture, politics, activism, and theater, and Bangkok was no exception.

The next International AIDS Conference will be held in Toronto in 2006. The 3rd IAS Conference on HIV Pathogenesis and

Treatment, which focuses on basic and clinical science, will be held in Rio de Janeiro in 2005.

#### Clinical Trials of Antiretroviral Therapy

##### Tenofovir vs Stavudine: Final 3-Year Results

Few new clinical trials were presented in Bangkok, but longer-term data were presented from a number of major studies, including GS 903, the only large 3-year, randomized, double-blind trial of antiretroviral therapy ever conducted [Gallant JE, et al. Abstract TuPeB4538]. In this trial, 600 treatment-naïve patients were randomized to receive either tenofovir DF (TDF) or stavudine (d4T) in combination with lamivudine (3TC) and efavirenz (EFV). The virologic outcomes at the end of the 3-year study were excellent in both arms: 73% and 69% of the TDF and d4T recipients achieved a viral load of <50 c/mL by intent-to-treat (ITT), missing=failure (M=F) analysis, the best results observed in any large randomized trial to date. However, there were important differences in toxicity between the two arms. Patients in the d4T arm had significantly higher fasting triglyceride and LDL cholesterol levels ( $P<0.01$ ), and the difference in fasting triglycerides continued to increase throughout the 3-year study period. These differences were clinically as well as statistically significant: By the end of the study, 16% of d4T recipients were taking a lipid-lowering agent compared to 5% of those taking TDF ( $P<0.001$ ). Not surprisingly, peripheral neuropathy was significantly more common in those taking d4T: 31 (10%) of 301 in the d4T group compared to 9 (3%) of 299 patients in the TDF group ( $P<0.001$ ). Similarly investigator-

defined lipodystrophy was more frequent with d4T, and occurred in 19% and 3% of d4T and TDF recipients, respectively ( $P<0.001$ ). The investigators' assessment of lipodystrophy was supported by objective measures as well: Total limb fat as measured by DEXA was higher in TDF-treated patients at both 96 and 144 weeks ( $P<0.001$ ), and the differences between arms increased during the final year of the study. In addition, patients on TDF had gained an average of 2.9 kg from baseline at 144 weeks compared to 0.6 kg in d4T recipients ( $P=0.001$ ). No significant renal toxicity was observed in either arm. Patients in both arms experienced a statistically significant decline in bone mineral density at the hip and spine during the first year, which appeared to level off over the second and third years of the study. At 144 weeks, bone loss was greater among TDF recipients in the spine ( $P=0.001$ ) but not in the hip ( $P=0.064$ ). The clinical significance of this bone loss is unclear, however, as it ranged from 1.0% to 2.8% loss from baseline. There were actually more fractures in the d4T arm, though all but one were traumatic and not felt to be due to osteopenia.

NNRTI resistance mutations and M184V were the most common mutations observed among patients failing therapy in

*continued on page 2*

#### Inside This Issue

Women and HIV in the Spotlight . . . . .	7
Management of Community-Associated Methicillin-Resistant <i>Staphylococcus aureus</i> Infections in the Outpatient Setting . . . . .	10



## XV International AIDS Conference in Bangkok: Antiretroviral Therapy

continued from page 1

both arms. Among those who failed therapy on the TDF arm, 7 developed K65R in the first year of therapy and 1 in the second year. No patient developed K65R in the third and final year of the trial. Thus K65R was present in approximately 17% of the TDF recipients who failed therapy and in less than 3% of the total number of patients treated with TDF.

In a sub-analysis of the women participating in GS903, DeRuiter found that the virologic response was similar between men and women, though women had a greater increase in CD4 count [Abstract MoOrB1083]. Men taking d4T were much more likely to have significant increases in fasting triglycerides than women. Women experienced greater losses in bone density than men, though there were no fractures among women.

These results, also published during the same week [*JAMA* 2004;292:191], are important because they demonstrate the potency and durability of two simple regimens, one of which (TDF/3TC/EFV) is now available as a once-daily regimen. They also show clear differences in toxicity between the two arms, without a significant cost in terms of drug resistance. The results have been extrapolated, by clinicians, the FDA, and the IAS-USA Guidelines Panel, to the combination of TDF + emtricitabine (FTC) + EFV, and the fixed-dose coformulation of TDF/FTC (*Truvada*) was recently approved by the FDA.

### CLASS: 96-Week Data

John A. Bartlett from Duke presented 96-week data from the CLASS study, a comparison of EFV, ritonavir-boosted amprenavir (APV/r), and d4T, each combined with a nucleoside backbone of abacavir (ABC) + 3TC [Abstract TuPeB4544]. In contrast to earlier presentations of the data, where the EFV regimen was associated with better virologic responses (proportion with VL <400 c/mL by ITT analysis) than the d4T or APV/r regimens, the 96-week data showed no difference in virologic suppression to <400 c/mL by ITT, M=F analysis. However, the d4T arm was inferior by on-treatment analysis, and also by ITT M=F analysis in patients with baseline viral

loads >100,000 c/mL. Duration of suppression was significantly longer in the EFV arm than in the d4T arm (P=0.007). Of the three CLASS regimens, only the EFV-based combination is still widely used today. This study, along with a number of others using a variety of regimens, supports the use of the ABC/3TC nucleoside backbone, which is now available as an FDA-approved fixed-dose coformulation (*Epzicom*).

### Efavirenz vs Indinavir: 3-Year Data from the 006 Trial

Karen Tashima presented the final 3-year data from DuPont 006, an early study that compared EFV and indinavir (IDV), both given in combination with zidovudine (AZT) and 3TC [Abstract TuPeB4547]. CD4 counts continued to rise throughout the treatment period, and after 3-years of therapy, approximately half of the EFV-treated patients had viral loads <400 c/mL, which was significantly better than the results for the IDV-treated patients. While this is a lower rate of suppression than was seen in the GS 903 study, approximately 15% of those in the 006 trial had received prior nucleoside analog therapy, whereas those in the GS 903 trial were all treatment-naïve.

### Fosamprenavir Studies in Treatment-Naïve Patients

Edwin de Jesus presented 48-week data from the SOLO trial, a comparison of once-daily ritonavir-boosted fosamprenavir (FPV/r) vs twice-daily nelfinavir (NFV), both combined with an ABC/3TC backbone given twice daily in treatment-naïve patients [Abstract TuPeB4503]. While the overall results were comparable, *post-hoc* analyses demonstrated that patients with high viral loads and low CD4 counts appeared to have better responses to FPV/r than to NFV, and the 48-week virologic response to FPV/r (suppression to <400 c/mL) was not affected by baseline viral load or CD4 count, in contrast to the NFV arm. It is unclear whether these differences are statistically significant, however, because the study was not powered to demonstrate differences in these *post-hoc* analyses. Patients who developed virologic failure in the FPV/r arm had no evidence of protease

inhibitor (PI) resistance and less nucleoside analog reverse transcriptase inhibitor (NRTI) resistance than those who failed in the NFV group. The differences in resistance appeared to be more pronounced among those with low CD4 counts and high viral loads at baseline. These results are consistent with those from several lopinavir/ritonavir (LPV/r) trials in PI-naïve patients. To date no PI resistance has been observed in patients failing LPV/r in these trials, including the 720 study, in which no PI or thymidine analog resistance has been observed after 5-years [Hicks C, et al. Abstract WeOrB1291], and the 863 trial, which demonstrated no PI resistance and significantly less NRTI resistance in the LPV/r arm compared to the NFV arm [Walmsley SL, et al. *N Engl J Med* 2002; 346:2039-46]. It now appears that PI resistance can occur in PI-naïve patients failing therapy, but the fact that these cases are rare enough to be publishable is remarkable.

While FPV/r was administered once a day in this trial involving treatment-naïve patients, it should be noted that in treatment-experienced patients enrolled in the CONTEXT trial, efficacy of once-daily FPV/r (1400/200 mg qd) was inferior to that of twice-daily FPV/r (700/100 mg bid) [Elston, et al. Abstract MoOrB1055]. Unboosted FPV was superior to NFV in treatment naïve patients in the NEAT trial [Brutus A, et al. Abstract TuPeB4500], in puzzling contrast to the overall results of the SOLO trial, in which unboosted FPV and NFV were comparable. Nevertheless, boosted FPV is likely to be preferred over unboosted FPV, given the better resistance profiles among patients who fail therapy and the high cost of unboosted FPV.

### Enfuvirtide: 96-Week Results from the TORO Trials

Arasteh presented 96-week results from the TORO studies, the pivotal multinational trials in treatment-experienced patients that led to the approval of enfuvirtide (ENF, T-20) [Abstract MoOrB1058]. These long-term results demonstrated durability of response in patients randomized to take ENF along with an optimized background



## XV International AIDS Conference in Bangkok: Antiretroviral Therapy

(OB) regimen. Since patients in the control (OB alone) arm crossed over and added ENF at 48 weeks, the data at 96 weeks are not controlled. Over half of those randomized to the ENF + OB arm remained on therapy at 96 weeks, which is impressive given the fact that this was a highly treatment-experienced group. The 96-week data demonstrate that the majority of patients whose viral loads were suppressed at week 48 maintained suppression at week 96, using both the 400 c/mL and the 50 c/mL threshold, and CD4 counts remained fairly stable. These data support the durability of response to ENF in patients who have a short-term response to therapy, and emphasize the importance of using this drug

in combination with other active drugs whenever possible.

### Monotherapy for Virologic Suppression

Several studies looked at the once radical idea of monotherapy with LPV/r in treatment-naïve patients. Gathe reported 48-week results from the IMANI-1 study, in which 30 patients initiated treatment with LPV/r alone [Abstract MoOrB1057]. A higher dose of LPV/r (533/133 mg bid) was used in those who weighed more than 70 kg. Ten of the 30 discontinued therapy, mostly for reasons unrelated to treatment. Of the 20 who remained on therapy, all had a viral load <400 c/mL at 48 weeks (90% <50 c/mL). Thus, by ITT, non-completer=

failure (NC=F) analysis, suppression to <400 c/mL and <50 c/mL was achieved in 67% and 60%, respectively. Mean CD4 count increase was 317 cells/mm<sup>3</sup> at 48 weeks.

Arribas presented the results of the Only *Kaletra* (OK) study, a 24-week randomized, open-label, multicenter study from Spain in which 42 patients who were on an LPV/r-based regimen for at least one month with CD4 counts >800 cells/mm<sup>3</sup> and viral loads <50 c/mL for at least 6 months, were randomized to remain on LPV/r + 2 NRTIs or to switch to LPV/r monotherapy [Abstract TuPeB4486]. All patients who remained on

*continued on page 4*

# THE HOPKINS HIV REPORT

## EDITORIAL BOARD

**John G. Bartlett, M.D.**

*Professor of Medicine; Director, Division of Infectious Diseases; Director, Johns Hopkins University AIDS Service*

**Joel N. Blankson, M.D., M.P.H.**

*Assistant Professor, Medicine*

**Emily J. Erbeling, M.D., M.P.H.**

*Assistant Professor of Medicine, Epidemiology, and Pediatrics*

**Joel E. Gallant, M.D., M.P.H.**

*Associate Professor of Medicine and Epidemiology; Associate Director, Johns Hopkins University AIDS Service*

**Kelly A. Gebo, M.D., M.P.H.**

*Assistant Professor of Medicine and Epidemiology*

**Jeanne Keruly, M.S., C.R.N.P.**

*Instructor, Medicine*

**Gregory M. Lucas, M.D.**

*Assistant Professor of Medicine*

## CONTRIBUTING EDITORS

**Jean R. Anderson, M.D.**

*Associate Professor of Obstetrics, Gynecology, and Medicine*

**Richard E. Chaisson, M.D.**

*Professor of Medicine, Epidemiology, and International Health*

**Joseph Cofrancesco, Jr., M.D., M.P.H.**

*Assistant Professor of Medicine*

**James P. Dunn, M.D.**

*Associate Professor of Ophthalmology*

**Charles W. Flexner, M.D.**

*Associate Professor of Medicine, Pharmacology and Molecular Science, and International Health; Associate Director of Graduate Training Program in Clinical Investigation*

**Rajesh T. Gandhi, M.D.**

*Instructor in Medicine, Partners AIDS Research Center Massachusetts General Hospital Boston, MA*

**Douglas A. Jabs, M.D.**

*Professor of Ophthalmology and Medicine*

**Brooks Jackson, M.D.**

*Professor of Pathology; Deputy Director for Clinical Affairs, Department of Pathology*

**Ciro R. Martins, M.D.**

*Assistant Professor of Dermatology*

**Justin C. McArthur, M.B., B.S., M.P.H.**

*Professor of Neurology and Epidemiology*

**Richard D. Moore, M.D.**

*Professor of Medicine and Epidemiology*

**Thomas C. Quinn, M.D.**

*Professor of Medicine, International Health, Molecular Microbiology and Immunology*

**Robert Siliciano, M.D., Ph.D.**

*Professor of Medicine, Molecular Biology and Genetics*

**Timothy R. Sterling, M.D.**

*Associate Professor of Medicine, Vanderbilt University Medical Center*

**Glenn J. Treisman, M.D., Ph.D.**

*Associate Professor of Psychiatry and Medicine*

## NEWSLETTER STAFF

**Richard Dunning, M.H.S.**

*Managing Editor*

**Lisa Darrah, B.A.**

*Design and Production*

**Sharon M. McAvinue**

*Business Development*

Visit The Johns Hopkins AIDS Service Website:  
<http://www.hopkins-aids.edu>

## SUPPORT

The Hopkins HIV Report is published six times per year by The Johns Hopkins University AIDS Service, Division of Infectious Diseases. Publication of this newsletter is underwritten by a generous grant from GlaxoSmithKline; we gratefully acknowledge their support.

©2004 The Johns Hopkins University AIDS Service, Division of Infectious Diseases. Permission to use and reproduce portions of this newsletter is hereby granted, provided that author and publication are fully credited and both the copyright and permission notice appear. All other rights reserved.

Canada Post Publications Sales Agreement  
# 40683044



## XV International AIDS Conference in Bangkok: Antiretroviral Therapy

continued from page 3

combination therapy maintained a viral load <50 c/mL at week 24. In contrast, there were three participants (14%) who experienced virologic failure among the 21 randomized to LPV/r monotherapy, with the remainder of the patients maintaining virologic suppression. Interestingly, lopinavir trough concentrations were adequate in 2 of the 3, and none of the patients had demonstrable PI resistance. Virologic suppression was achieved with reintroduction of the original NRTIs. Similarly, in a report of 19 patients treated with LPV/r monotherapy following virologic suppression on HAART, there was one case of unexplained virologic failure [Ruane P, et al. Abstract TuPeB4577], and in Gathe's IMANI study, one patient failed to achieve complete virologic suppression on

LPV/r monotherapy despite excellent LPV levels and no evidence of PI resistance. His virus became suppressed when his regimen was intensified with tenofovir and lamivudine. There was also one unexplained virologic failure in a study of 18 patients who switched from a stable NNRTI-containing regimen to LPV/ monotherapy [Pierone G, et al. Abstract TuPeB4595]. The reasons for these anecdotal unexplained failures with LPV/r monotherapy remain unclear. One hypothesis is that there may be anatomic or pharmacologic "compartments" that PIs can't penetrate. If this were the case, it would be a major obstacle to the idea of monotherapy, at least with PIs. Nevertheless, none of these failing patients appears to have developed resistance as a result of monotherapy failure, and larger trials of this still investigational strategy are ongoing.

### Monotherapy to Prolong Treatment Interruption

The M184V mutation, which emerges in patients failing 3TC- or FTC-containing regimens, is known to decrease viral replicative capacity (RC), potentially slowing clinical and immunologic progression. For this reason, the usual dictum is that 3TC or FTC should be maintained in patients taking a non-suppressive regimen, though this concept has not been carefully studied. Castagna presented data from a small but intriguing study in which patients known to have an M184V mutation who were intending to interrupt therapy with a failing regimen (viral load >1000 c/mL) were randomized either to stop therapy completely or to continue 3TC alone [Abstract WeOrB1286]. Preliminary 24-week data demonstrated a number of distinct advantages to continuing 3TC, including a significantly slower decline in CD4 count and a lower viral load rebound after discontinuing HAART. The proposed mechanism was supported by the fact that replication capacity remained low in those who remained on 3TC but increased substantially in those who stopped all therapy. Moreover, not only was the M184V mutation maintained in the monotherapy group, but other reverse

transcriptase mutations persisted as well, suggesting linkages of mutations on the same virions. Therefore, the magnitude of benefit might not have been the same had 3TC been restarted following a period of time off therapy, since it would have selected only 3TC-resistant mutants without other mutations.

Of course, the other advantage of this approach is that it has no clear downside: No new mutations emerged as a result of 3TC monotherapy, nor would any be expected. M184V causes such high-level resistance to 3TC that there is little reason for the virus to develop additional mutations despite continued therapy. However, an important caveat, aside from the small sample size and the preliminary nature of the results, is that these were not "salvage" patients: They all had CD4 counts above 500 cells/mm<sup>3</sup> and were stopping for a variety of reasons that did not necessarily have anything to do with treatment failure. Despite the benefits of 3TC monotherapy, their CD4 counts still declined. Such a strategy might not be appropriate for patients at more advanced stages of disease, for whom more aggressive salvage regimens might be required, even if they weren't fully suppressive. Instead, it might best be viewed as a way to delay the need for resumption of HAART in patients who are stopping therapy with high CD4 counts. At the present time it should be considered only in those who have already developed the M184V mutation, though this study raises the intriguing question of whether there might be a benefit to this approach even in treatment-naïve individuals. Would a long delay in the need for HAART ever justify sacrificing 3TC and FTC as active antiretroviral agents?

### Treatment Interruption Studies

...and speaking of treatment interruption, there were a number of presentations on intermittent therapy, especially those involving so-called "CD4-guided approaches," in which patients doing well on HAART stop therapy; restarting based on a predetermined fall in CD4 count. In the HIV-NAT 001.4 trial,

#### EDITORIAL POLICY & DISCLAIMER

Organizations providing financial support do not participate in the editorial process or otherwise influence editorial decisions. The information presented in *The Hopkins HIV Report* represents the standards of care of the Johns Hopkins University AIDS Service. Every effort is made to ensure the timeliness and accuracy of information presented in this newsletter, but standards of care change rapidly; therefore, the authors, editors, and publisher will not in any way be held liable for the timeliness of information or for errors, omissions, or inaccuracies in this publication. Readers should review carefully the product information contained in manufacturers' package inserts for any drug mentioned in this publication; mention of products does not constitute endorsement.

#### THE HOPKINS HIV REPORT (HHR) IS FREE IN PRINT AND ONLINE

- **View** the current and archived newsletters online at <http://hopkins-aids.edu/publications.html>
- **Subscribe online** to receive the print version of *The Hopkins HIV Report*.
- **Change of address?** Complete the online form using the website address above *or* let us know by sending a postcard with your old (very important) and new address, plus the subscription number (located above your name and address on the HHR mailing label) to:  
*The Hopkins HIV Report*, Change of Address  
P.O. Box 651266  
Potomac Falls, VA 20165-1266
- **All other correspondence:**  
Email: [hivreport@jhmi.edu](mailto:hivreport@jhmi.edu) or write:  
*The Hopkins HIV Report*  
JHU ID @ Lighthouse Point  
2700 Lighthouse Point East, STE 220  
Baltimore, MD 21224

**Please note:** The HHR is published every other month— January, March, May, July, September, and November.



## XV International AIDS Conference in Bangkok: Antiretroviral Therapy

a small pilot study conducted in Thailand, patients on stable antiretroviral therapy with CD4 counts above 350 cells/mm<sup>3</sup> were randomized either to continue HAART, to switch to a one-week-on, one-week-off schedule, or to stop therapy until the CD4 count fell below 350 cells/mm<sup>3</sup> [Ananworanich J, et al. Abstract WeOrB1283]. The one-week-on, one-week-off arm was terminated early because of a high rate of virologic failure. However, at the end of the 96-week study period, there was no significant difference in virologic failure (viral load >500 c/mL) between the continuous therapy arms or the CD4-guided arm. While CD4 counts were higher among those randomized to receive continuous therapy, there was no difference in the proportion of patients who maintained CD4 counts above 350 cells/mm<sup>3</sup>. And in contrast to patients on continuous therapy, those in the CD4-guided arm spent only 46% of the study period on HAART. While this was not associated with measurable differences in quality of life, it clearly has important cost implications, which are especially relevant in developing countries.

This strategy was supported by a number of other studies presented in Bangkok, most of which found that therapy could be safely interrupted in some patients doing well on HAART, but confirmed findings from prior observational studies regarding predictors of successful interruption [Ruiz L, et al. Abstract TuPeB4567; Mussini C, et al. Abstract TuPeB4569; Katzentstein DA, et al. Abstract TuPeB4585]. Specifically, patients with relatively higher CD4 nadirs were able to remain off therapy longer than those who began HAART with lower CD4 counts. Other predictors included lower pre-HAART viral load and longer duration of virologic suppression on HAART. These findings raise questions about our current guidelines for initiation of therapy in naïve patients. By waiting until the CD4 count is between 200 and 350 cells/mm<sup>3</sup>, are we essentially committing our patients to continuous therapy for life? Perhaps earlier initiation of therapy in naïve patients would allow many to take therapy intermittently,

resulting in less cumulative time on HAART and less long-term toxicity.

On the other hand, there are a number of potential drawbacks to intermittent therapy. Viral rebound increases the risk of transmission. Discontinuation of therapy may place patients at risk for drug resistance, especially with regimens containing NNRTIs, which have long half-lives and are vulnerable to high-level resistance with single point mutations. And while short-term data from cohort studies show no clear disadvantage to remaining untreated with a CD4 count above 350 cells/mm<sup>3</sup>, that could change with longer-term data. For example, while the risk of opportunistic infections is minimal above that threshold, there may be an increased long-term risk of lymphoma or neurologic complications. Data from the GS 903 trial, among others, suggest that bone mineral density decreases with initiation of antiretroviral therapy. If that's true for all regimens, what are the long-term consequences of repeated starts and stops? Allowing the CD4 cell count to decline before starting or resuming therapy may increase the likelihood of a shift from an CCR5-tropic virus to a CXCR4-tropic virus or a mixed X4/R5 phenotype [Harrigan PR, et al. Abstract MoPeB3117], which will become increasingly relevant with the development of new CCR5 antagonists [See also, Shepherd J and Quinn T, *HHR* 2004;16(4):1]. Finally, as antiretroviral therapy gets safer and easier, the risk:benefit ratio may shift in favor of earlier continuous antiretroviral therapy, despite the apparent short-term safety of CD4-guided treatment interruption strategies.

### Induction-Maintenance Strategies

Marty Markowitz from the Aaron Diamond Research Center presented data from a large trial in which 448 patients were started on a regimen of AZT/3TC/ABC + EFV [Abstract LbOrB14]. Those who had viral loads below 50 c/mL at 1 year were randomized to continue 4-drug therapy or to discontinue EFV and remain on the triple-NRTI combination for another

48 weeks. Unfortunately, interpretation of the results of this study is complicated by the fact that almost 40% of the participants dropped out of the study during the first year of therapy prior to randomization. Nevertheless, the results demonstrated that overall efficacy of the simplified maintenance regimen was non-inferior to the 4-drug combination by an intent-to-treat analysis. On the other hand, virologic failure was more common in the triple-NRTI arm (11% vs 6%), which was balanced out in the ITT analysis by a higher drop-out rate in the EFV-containing arm. Patients failing therapy on the EFV-containing arm tended to have 3TC and EFV resistance (M184V and K103N), while those failing triple-nucleoside therapy typically had M184V and thymidine analog mutations. The high drop-out rate and the higher rate of virologic failure in this study make it hard to use these results to guide clinical practice. Nevertheless, it seems clear that response to triple-NRTI therapy may be better in patients whose viral load is already suppressed on a standard HAART regimen than in those who start therapy with a triple-NRTI regimen. For now, the question of whether we can safely “deintensify” therapy after achieving virologic suppression remains open.

It is worth noting that a meta-analysis of studies comparing 4- vs 3-drug regimens for initial therapy showed no advantage of a fourth drug [Moyle GK, et al. Abstract TuPeB4519]. We are all eagerly awaiting the final results of ACTG 5095, which will compare AZT/3TC + EFV and AZT/3TC/ABC + EFV. Will the addition of a third NRTI further improve the efficacy of an already highly effective regimen?

### Other Triple-NRTI Regimens

The high rate of virologic non-response associated with the triple-NRTI regimen of ABC, 3TC, and TDF has been documented in three clinical trials and has been discussed in previous issues of *The Hopkins HIV Report*. Recent data suggest that the failure

*continued on page 6*



of this regimen was not due to an intracellular interaction or antagonism between ABC and TDF [Hawkins T, et al. Abstract TuPeB4627; Miller JD, et al. Abstract WeOrB1237]. The favored hypothesis of the day is the low genetic barrier to resistance: both ABC and TDF exert selective pressure on K65R, which decreases susceptibility to all three drugs in the regimen. In a poster presentation, results from studies examining a variety of ABC/3TC-containing regimens were analyzed, including the triple-NRTI combination of ABC/3TC/AZT [Gallant JE, et al. Abstract TuPeB4502]. Non-response ranged from 0% to 24% across the trials, in sharp contrast to the 74% observed in ESS 30009, the largest of the ABC/3TC + TDF trials, pointing out that not all triple-NRTI regimens are the same and supporting the viability of the ABC/3TC backbone in other combinations.

### Cohort Studies

Egger presented the results of a meta-analysis of 13 different studies from 12 cohorts comprising the large Antiretroviral Therapy Cohort Collaboration (ART-CC), representing over 60,000 person-years of follow-up [Abstract TuOrC1157]. The analysis looked at changes in survival between 1995 and 2003. Mortality rates declined between 1995 and 1998 as a result of HAART, but did not decrease further between 1998 and 2003. In fact, in some cohorts, primarily those with a large proportion of injection drug users, mortality and development of new AIDS diagnoses increased during that time period, whereas there was a further decrease in these outcomes among men who have sex with men.

Data from the EuroSIDA cohort assessed the durability of virologic suppression among patients who achieved an undetectable viral load on their initial HAART regimen [Phillips A, et al. Abstract TuPeB4542]. Patients treated with nelfinavir-based regimens were more likely to experience virologic rebound than those treated with efavirenz. While this was also true of nevirapine- and abacavir-based

triple-NRTI regimens in patients with prior pre-HAART nucleoside analog therapy, it was somewhat surprising that treatment-naïve patients treated with triple-NRTI regimens were no more likely to rebound than those treated with efavirenz, in contrast to other studies, including ACTG 5095.

A retrospective case-control study using mortality data from San Francisco found that patients initially treated with the four “3x5 regimens” recommended by the WHO for use in developing countries (AZT/3TC or d4T/3TC plus either EFV or NVP) had the best survival compared to those treated with other regimens (mostly unboosted PI-based combinations) [Chen SY, et al. Abstract MoOrC1082]. This study offers support for the choice of regimens by the WHO. However, the ability to generalize these findings is limited by the lack of follow-up regimens in many developing countries. In addition, the study design is subject to selection bias: NNRTI-based regimens may have been more widely used by more experienced clinicians or may have been prescribed to patients more likely to adhere to therapy.

### Complications of HIV Infection and Antiretroviral Therapy

A few brief bullets on complications associated with HIV infection and its treatment:

- Hypogonadism was an independent risk factor for gynecomastia in HIV-infected men [Blanco JL, et al. Abstract ThOrB1357].
- Longer duration of antiretroviral therapy was found to be an independent predictor of risk for osteonecrosis in a large French database [Mary-Krause M, et al. Abstract ThOrB1358]
- Discoloration of the skin, nails, or tongue was observed in 4% of patients enrolled in phase 3 trials involving FTC [Mondou E, et al. Abstract WePeB5916]. This was slightly more than was observed in the control groups, and was more common among black patients. Skin discoloration did not lead to discontinuation of therapy, and it resolved spontaneously in 17%.
- In patients with lipodystrophy on HAART, the combination of an exercise program plus

oxandrolone was associated with increased fat-free mass and functional capacity compared to exercise alone, but at the cost of higher total and LDL cholesterol levels and lower HDL cholesterol levels [Smith BA, et al. Abstract MoOrB1059].

- Several retrospective analyses of renal function in TDF-treated patients found little evidence of significant renal toxicity [Scott J, et al. Abstract TuPeB4632; Lewis S, et al. Abstract TuPeB4599]. Three-year renal safety was confirmed in the GS 903 study, where there were no discontinuations due to renal toxicity and no differences in renal abnormalities between the TDF and d4T arms [Staszewski S, et al. Abstract WePeB5917].
- ABC hypersensitivity reactions (HSR) were reported in 9% of patients taking once-daily ABC and 7% of those taking twice-daily ABC in the ZODIAC study [Hernandez J, et al. Abstract TuPeB4521]. The current package insert for ABC and ABC-containing coformulations states that ABC HSR occurs in approximately 8% of ABC-treated patients.
- Data from the BMS 034 trial comparing atazanavir (ATV) to EFV found that there was little difference in fat gain between the two arms [Noor MA, et al. Abstract WePeB5874]. Patients who were underweight and insulin-sensitive at baseline were more likely to gain adipose tissue, and older patients were more likely to gain visceral adipose tissue, a normal pattern with aging.

### Conclusions

Those of us attending the “Track B” clinical sessions couldn’t help but feel that we were on the sidelines, missing out on the real “action” of the conference. That is, the politics, the epidemiology, and the discussions of treatment delivery in the developing world: what’s working, what’s not, and what remains to be done. Since the groundbreaking XIII conference in Durban in 2000, where treatment of HIV infection in resource limited countries was taken seriously for the first time, we have made some progress, but we have a long, long way to go before we come close to realizing the goal expressed in the theme of the Bangkok conference: “Access for All.” ▲



## XV International AIDS Conference: Women and HIV in the Spotlight

By Jean R. Anderson, M.D.

The theme for the XV International AIDS Conference in Bangkok was "Access for All" and UN secretary general Kofi Annan made it clear in his address at the opening ceremonies that without HIV strategies focusing specifically on women, there can be no global progress in fighting the disease. Noting that women now constitute nearly half of all people infected with HIV globally, a new UN report released in time for the conference, "Women and HIV/AIDS: Confronting the Crisis," documents the often invisible impact of AIDS on women and girls and highlights the ways discrimination, poverty and gender-based violence help fuel the epidemic.

The scientific program also reflected a greater emphasis on issues of importance for women in prevention and treatment than in past conferences.

### Prevention for Positives

The CDC has recently placed increased emphasis on targeting prevention efforts to HIV-infected individuals, focusing on safer sexual and drug-using behaviors. In an analysis from the Women's Interagency HIV Study (WIHS) of sexual behavior in over 1500 women living with HIV over a one-year period, Wilson and colleagues found that 29% of women reported more than one sexual partner and 35% reported at least one new sexual partner during this time period [Abstract MoPeD3982]. Consistent condom use was reported two-thirds of the time in newer partnerships but in slightly less than half of more established relationships. Among new partnerships neither partner was aware of the other's HIV status in 39% of cases, as compared to 14% in more established relationships. Furthermore, newer partnerships were less likely to be concordant (18% vs 27%,  $p < .05$ ). A little closer to home, Temoshok and Wald surveyed 131 patients (44% women) from an inner-city Baltimore HIV clinic and found that 66% reported a recent partner of negative or unknown HIV status, and 34% acknowledged inconsistent condom use during vaginal sex [Abstract TuPeB4680]. Both of these studies highlight

the ongoing challenges and the responsibility HIV clinicians and programs face in promoting a prevention agenda. Although this applies to both men and women with HIV, women will require special strategies that recognize and address gender-specific sociocultural, economic and childbearing issues, as well as other vulnerabilities related to violence and depression.

### Thinking About Pregnancy

Two presented studies have implications for preconception counseling and care for HIV-infected women. The European Collaborative Study, a cohort study established in 1985, examined subsequent childbearing in over 3900 women and found that since prevention of mother-to-child transmission (PMTCT) interventions have been available, there has been a significant increase in pregnancies. An estimated 4.4% of women enrolled in the pre-HAART era (1990-1994) had a second baby within 36 months of their first; this increased to 16.7% for those enrolling in 1995-1999 ( $p < 0.002$ ) [Thorne C, et al. Abstract ThPeC7291]. In a study of the epidemiology of adolescents living with HIV in New York City, Liu and colleagues reported that among 1506 adolescents, 51% were female and over two-thirds were perinatally infected [Abstract TuPeC4769]. The number of adolescents with perinatally-acquired HIV will likely increase with time due to improved treatment and survival. However, these patients will have special needs and challenges as they approach issues related to childbearing, such as those related to extensive antiretroviral exposure, both from treatment and from prophylactic exposures *in utero* and after birth. Both of these studies highlight the need for providers to engage their patients in discussions about childbearing and to ensure appropriate referrals for preconception counseling and care in those patients or couples considering pregnancy.

### Pregnancy

**Missed Opportunities:** The primary focus of studies of HIV in pregnancy continues to be

prevention of mother-to-child transmission. With currently available interventions, there have been dramatic decreases in perinatally acquired HIV infection and it is possible to achieve transmission rates of 1-2%. However, the CDC estimates that there continue to be 280-370 infants born annually with HIV infection in the U.S. In most cases these infections do not represent failures of the interventions but missed opportunities to utilize them. The most common missed opportunities include failure to offer or accept HIV testing during prenatal care; diagnosis of HIV without delivery of appropriate antiretroviral treatment or prophylactic therapy; or lack of prenatal care and unknown HIV status. Among 2,600 HIV-exposed infants delivered 1997-2001 in New York, transmission occurred in 2% of deliveries in which combination ART during the prenatal period was combined with intrapartum and neonatal ZDV [Peters V, et al. Abstract ThPeC7288]. A major new CDC initiative has recently been launched to offer rapid HIV testing in labor for women who present with unknown HIV status, so that intrapartum and/or postpartum ARV prophylaxis can be offered to reduce transmission risk. In a report of the multicenter Mother-Infant Rapid Intervention at Delivery (MIRIAD) study, Bulterys and coworkers reported on 5744 women who were approached for testing [Abstract ThPeB7027; *JAMA* 2004;292:219]. Of these women, 84% consented to HIV testing and the prevalence rate was 0.7%. The sensitivity and specificity of the rapid test (*Oraquick*) were 100% and 99.9%, respectively and the positive predictive value was 90%, compared to 76% with enzyme immunoassay. The median time from blood collection to patient notification of results was 66 minutes. Equal proficiency was seen whether *Oraquick* was performed in the laboratory or at the point of care. All hospitals where deliveries take place should review this study and consider putting protocols in place to incorporate rapid testing into labor and delivery practice.

*continued on page 8*



## XV International AIDS Conference: Women and HIV in the Spotlight

continued from page 7

### Pharmacokinetics of Antiretroviral Agents

**in Pregnancy:** There is increasing recognition that pregnancy may alter the pharmacokinetics of antiretroviral agents as a result of changes in plasma volume, protein binding, metabolism and excretion. While there are still limited data in this area, several studies presented in Bangkok increased our understanding and may help guide clinical practice or suggest the need for further study. Among 19 pregnant women treated with saquinavir hard-gel capsules (*Invirase*) 1,000 mg boosted with ritonavir 100 mg bid, only one required an increase in saquinavir to 1200 mg to achieve adequate plasma exposure based on therapeutic drug monitoring and projected trough levels [Khan W, et al. ThPeB7064]. A German study found that nevirapine (NVP) plasma exposure, measured by area-under-the-curve concentration (AUC) and peak levels were significantly decreased in pregnant women on NVP-containing ART regimens compared to men after body weight adjusted analysis [Haberl A, et al. TuPeB4644]. Meanwhile, Thai data revealed that NVP drug levels, while variable, can be detected at concentrations high enough to select for resistance for up to 3 weeks after single-dose NVP given in labor for PMTCT [Cressey TR, et al. ThOrB1352]. The longest duration of detectable NVP levels was 19 days postpartum and median t<sub>1/2</sub> was 58.3 hrs (22.9-160.0).

Finally, in a late breaker session, Alice Stek reported preliminary PK results in a cohort of pregnant women receiving LPV/r 400/100 mg twice daily at 30-36 weeks gestation and at 6-12 weeks postpartum [Abstract LbOrB08]. Ten of 12 pregnant women and one of four postpartum women did not meet the target LPV AUC (>10th percentile LPV in non-pregnant historical controls). A study to evaluate increased LPV dose is planned.

Taken together these studies suggest that careful PK studies in pregnancy should be conducted with all ARV agents and that the additional potency and tolerability associated with boosted PI regimens may not necessarily translate into adequate blood levels during pregnancy. Obviously, more study is needed to evaluate alternative dosing strategies and the usefulness of TDM, as well as to assess

whether these lower blood levels are indeed associated with greater development of viral resistance and earlier clinical failure.

**Nevirapine Resistance:** A major concern about the use of NVP in PMTCT settings is the documented NVP resistance that occurs in 15-40% of mothers who receive single-dose NVP. This probably relates to the extended half-life seen with this drug, as noted above, and the low genetic barrier to resistance with NNRTIs. This is an issue not only for low resource settings implementing NVP-based PMTCT programs, but also for programs in developed countries that use NVP-based HAART regimens in pregnancy for prophylaxis in women who do not yet require ongoing ART. In other words, how do you stop NVP and other regimen components in order to prevent development of resistance? Another late breaker session presented by James McIntyre from South Africa addressed these concerns in the context of single-dose NVP PMTCT programs [Abstract LbOrB09]. The Treatment Options Preservation Study (TOPS) is an open-label study to determine whether adding 4 or 7 days of ZDV/3TC to single-dose NVP could reduce the rate of development of NNRTI resistance mutations. In a preliminary analysis of 61 women with six-week resistance data (all with clade C virus), lower rates of resistance were observed with the 4 or 7 day "tail" as compared to SD-NVP alone (9% vs 50%, p=0.001). These results are promising but are not conclusive and several factors should be noted in their consideration: the number of women analyzed was small; the PK studies showing NVP levels up to 3 weeks after birth suggest that an even longer "tail" may be necessary; and the baseline viral load of the SD-NVP group was higher than in the two ZDV/3TC groups. Higher viral load has been associated with increased likelihood of resistance and indeed the 50% resistance rate was higher than previously reported. This issue remains a key and urgent focus for further study.

**Infant Post-Exposure Prophylaxis:** One potential answer to the NVP resistance problem in the PMTCT setting is to give post-exposure prophylaxis only to the infant. If this strategy is effective, it could be employed both

in low resource settings and in developed countries when HIV status is not identified until labor. Taha and colleagues [*Lancet* 2003;362:1171] recently demonstrated that a combination of single-dose NVP and a one week course of ZDV resulted in a 7.7% transmission rate compared to 12.1% with infant NVP only (36% efficacy) in infants who were not infected *in utero*, as reflected by negative virologic testing at birth. At the Bangkok meeting Glenda Gray and coworkers reported on results of another clinical trial in South Africa in which infants were randomized to SD-NVP or six weeks of ZDV [Abstract ThPeB7063]. Again excluding those infants infected *in utero*, SD-NVP was superior to ZDV (7.9 % vs 13.1 %, p<0.06, n=718) at 12 weeks.

**Nevirapine Toxicity:** Toxicity does not seem to be a significant problem with single-dose NVP. However, recent studies have increased concerns about use of NVP as a component of HAART regimens given to pregnant women for prophylaxis. Recent analyses showed that women with CD4 counts >250 cells/mm<sup>3</sup> were approximately 11 times more likely to experience symptomatic hepatotoxicity, often associated with a rash, than women with lower CD4 counts. Three studies presented in Bangkok addressed toxicity issues with NVP in pregnancy. In a Brazilian cohort of 218 pregnant women who received NVP for 7 or more days, João and colleagues reported overall toxicity of 5.6%, approximately half of whom discontinued therapy with NVP [Abstract ThOrB1354]. HCV infection was significantly associated with an increased risk of toxicity. The mean CD4 count was >250 cells/mm<sup>3</sup> in women, both with and without toxicity. In a US cohort of 170 pregnant women on NVP-containing regimens, 11 (6.5%) developed toxicity requiring discontinuation; of these, 6 had hepatic and 5 had dermatologic toxicity. NVP toxicity was associated with CD4 >250 cells/mm<sup>3</sup> [Gonzalez-Garcia A, et al. WePeB5918]. Finally, in a prospective cohort of 522 pregnant women in Spain on a variety of different regimens, adverse events were seen in 67 women (12.8 %) [Gonzalez Tome MI, et al. Abstract ThPeB7114]. However, most were mild-to-moderate; increases in liver



## XV International AIDS Conference: Women and HIV in the Spotlight

enzymes were observed in 10% of women with no differences seen between NVP-containing regimens versus other regimens and no differences with respect to CD4 count, viral load or HCV-coinfection between NVP and PI-based regimens. The topic of NVP toxicity will continue to be followed closely, but data to date have resulted in a change in the USPHS pregnancy guidelines recommendations.

**Mode of Delivery:** The appropriate role of cesarean delivery in PMTCT continues to be debated. An updated report from the European Collaborative Study on approximately 500 women with undetectable viral load, elective cesarean delivery reduced risk of transmission, but this was not significant on multivariate analysis when adjusted for ART use [Thorne C, et al Abstract ThOrC1419]. On the other hand, Fortuny and colleagues, in a prospective study of children born to HCV-HIV co-infected mothers (N=260) found that elective cesarean delivery was significantly protective against HCV MTCT [Abstract ThPeB7055].

### Menopause

There has been much debate about whether women with HIV go through menopause at an earlier age or whether there is an association with immune status. In the largest investigation (1063 HIV-infected, 272 HIV-uninfected in the WIHS study) of objectively measured menopausal status in HIV-infected women, there was no association between FSH levels or menopause (defined as FSH >25 mIU/mL and amenorrhea for at least 6 months) and HIV status, CD4 count, HIV RNA levels, class C symptoms, or use of antiretrovirals [Cejtin HE, et al. Abstract WePeD6504].

### Gender Disparity

An analysis of medical record data from 5611 women and 14,061 men receiving care in 10 U.S. cities (1999-2001, CDC Adult/Adolescent Spectrum of HIV Disease project) demonstrated gender differences in OI rates and trends, with women having higher incidence of esophageal candidiasis and

CMV disease while men had higher incidence of KS, cryptococcosis and cryptosporidiosis. However, men had declining trends in these three OIs, as well as recurrent pneumonia, MAC, TB and wasting, while women only showed declining trends in invasive cervical cancer and TB. Also of concern, women with CD4 counts <350 cells/mm<sup>3</sup> or with history of AIDS defining illness were less likely to be prescribed HAART (70% vs 74% overall and 61% vs 67% in IDUs, p<.01) [McNaghten AD, et al. Abstract MoOrC1032]. These data appear to demonstrate that there are still significant disparities in access to care and prevention services for women.

One potential cause for differences between men and women in HAART use is depression, which is significantly more common in women. In another WIHS study depression was diagnosed by objective measures in 63% of over 2000 women with HIV [Cook JA, et al. Abstract TuPeB4548]. Controlling for a variety of factors, including CD4 and viral load, age, race, substance use, and income, patients treated for depression (antidepressants plus counseling or counseling alone) were more likely to report use of HAART than those who were not treated.

### Summary

The Bangkok conference highlighted a number of important issues relating to women and HIV. Presentations on prevention suggested that more needs to be done to address and help reduce high risk behaviors among HIV-infected women. Also, other studies suggest that women may have reduced access to HIV care and prevention services.

The complexity of prevention of mother-to-child transmission continues to be a major issue. Failure to diagnose HIV during pregnancy remains a major barrier to PMTCT, although the MIRIAD study shows that the use of rapid testing in labor is both feasible and accurate. The use of NVP in pregnancy as part of a treatment or prophylactic regimen is becoming increasingly controversial. There are growing concerns about resistance with use of single dose NVP or when NVP-containing regimens are

stopped after delivery because of the prolonged half-life and the low genetic barrier to resistance. There is also unease because of toxicity with chronic NVP use, especially in women with CD4 counts >250 cells/mm<sup>3</sup>. Pregnancy appears to have an effect upon the pharmacokinetics of antiretrovirals, and it appears that standard dosing of both LPV/r and NVP results in suboptimal drug levels, with potential concerns about inadequate viral suppression and increased risk of resistance. Finally, new data presented show that, contrary to conventional wisdom, HIV infection or HIV-related immunosuppression do not appear to be associated with early onset of menopause. ▲

#### U.S. FDA Approves *Truvada* and *Epzicom*, New Antiretroviral Coformulations

The FDA recently approved two fixed-dose, dual-nucleoside coformulations: *Truvada* (emtricitabine plus tenofovir disoproxil fumarate) and *Epzicom* (abacavir plus lamivudine) for use in combination with other antiretroviral regimens. The following are the product summaries:

##### *Truvada*

**Manufacturer:** Gilead Sciences, Inc

**Formulation:** Each tablet contains 200 mg of emtricitabine (FTC) and 300 mg of tenofovir DF (TDF).

**Cost:** \$27.62/tablet (AWP)

**Usual Adult Dose:** One tablet daily; take with or without food.

**Link to Package Insert:**

<http://www.truvada.com/fpi.pdf>

##### *Epzicom*

**Manufacturer:** GlaxoSmithKline

**Formulation:** Each tablet contains 600 mg of abacavir (ABC) and 300 mg of lamivudine (3TC)

**Cost:** \$26.40/tablet (AWP)

**Usual Adult Dose:** One tablet daily; take with or without food.

**Link to Package Insert:**

[http://us.gsk.com/products/assets/us\\_epzicom.pdf](http://us.gsk.com/products/assets/us_epzicom.pdf)



# Management of Community-Associated Methicillin-Resistant *Staphylococcus aureus* Infections in the Outpatient Setting

By Newton E. Kendig, M.D.

## Epidemiology

Methicillin-resistant *Staphylococcus aureus* (MRSA), an established nosocomial pathogen, has recently emerged as an important cause of skin and soft tissue infections among patients who have not been hospitalized. Though infections are not specifically associated with HIV-related immunosuppression, they co-exist in many risk groups seen by HIV providers and are becoming increasingly common in HIV practice. These community-associated MRSA (CA-MRSA) infections have frequently been identified through outbreak investigations affecting athletes, inmates, military recruits, and men who have sex with men [MMWR 2003;52(33):793, MMWR 2003;52(41):992, MMWR 2003; 52(05):88, and Zinderman C, et al. *Emerg Infect Dis* 2004;10:941]. Injection drug use, homelessness, and the prior use of antimicrobial agents within the previous 6 months have also been associated with CA-MRSA infections [Charlebois E, et al. *Clin Infect Dis* 2004;39:47, and Baggett H, et al. *Infect Control Hosp Epidemiol* 2003;24:397].

CA-MRSA strains are remarkably similar worldwide, differing from hospital-acquired MRSA strains in 1) their susceptibility to a variety of oral antibiotics (excluding  $\beta$ -lactams); 2) the presence of type IV staphylococcal chromosomal cassette *mec* (*SCCmec*); and 3) the presence of genes that encode certain toxins, such as Pantone-Valentine leukocidin. The origin of CA-MRSA strains is uncertain, but molecular typing studies of MRSA isolates in a large San Francisco health care network identified strains that had evolved both from existing hospital strains and *de novo* in the community [Charlebois E, et al. *Clin Infect Dis* 2004:47].

## Clinical Presentation

Patients with CA-MRSA infections may present with skin and soft tissue infections such as furuncles, deep-seated folliculitis, impetigo, abscesses, or ecthyma. During CA-MRSA outbreaks, patients have

frequently sought medical attention for a "spider bite," or a "sore." CA-MRSA can also cause serious systemic infections including pneumonia, osteomyelitis, septic arthritis, endocarditis, and sepsis. No differences in overall disease severity have been established between CA-MRSA and nosocomial MRSA infections. Persons with HIV infection may be at greater risk for CA-MRSA infections based on associated risk behaviors or the presence of conditions that may increase the risk of acquiring *Staphylococcus aureus* infections such as severe skin disease, diabetes, chronic renal failure on hemodialysis, recent surgery, or the need for indwelling catheters [Lowry F, *N Eng J Med* 1998;339:520]. In one 3-year longitudinal study in the Texas prison system, inmates with HIV infection were twice as likely to develop MRSA infections compared to inmates without HIV infection; however the potential role of MRSA-related risk factors was not evaluated [Baillargeon J, et al. *Clin Infect Dis* 2004; 38:e92].

## Treatment

The emergence of CA-MRSA infections further complicates the management of outpatients presenting with skin and soft tissue infections. One approach for evaluating these patients is outlined in Table 1. On initial assessment all skin infections should be carefully examined for cellulitis, fluctuance, crepitus, and sinus drainage. Incision and drainage is the treatment of choice, and antibiotics are often unnecessary. Whenever feasible, incision and drainage should be pursued as the initial treatment. Furuncles and small abscesses can be drained with local anesthesia; whereas surgical consultation is often indicated for larger abscesses and infections of the face or hands.

Any wound drainage should be sent for routine bacterial cultures and antibiotic sensitivities, since the etiology of these infections can not be differentiated clinically and treatment can be targeted by identifying the offending pathogen. In some cases, incision and drainage alone will

adequately resolve minor infections without antibiotic therapy.

Empiric antibiotic therapy is indicated for patients with large or multiple furuncles, soft tissue abscesses, cellulitis, deep-seated folliculitis, impetigo, ecthyma, systemic disease or symptoms, or who are otherwise at high risk for serious complications, such as patients with prosthetic valves or previously diagnosed endocarditis. Treatment should be adjusted based on culture data and antibiotic susceptibilities, however the optimal choice for treating any specific CA-MRSA infection is unknown, since no controlled trials have assessed whether *in vitro* antibiotic susceptibilities correlate with clinical response. A specific treatment regimen should therefore be made on a case by case basis after weighing: antibiotic susceptibilities, patient-specific factors, and the risks and benefits of various therapeutic options as outlined in Table 2, p 12. Antibiotic selection for CA-MRSA infections does not differ for patients with or without HIV infection.

CA-MRSA infections are resistant to  $\beta$ -lactam antibiotics, but are often susceptible to other available oral antibiotics such as trimethoprim-sulfamethoxazole and clindamycin that have comparable bioavailability. Consultation with the microbiology laboratory is indicated for CA-MRSA isolates that are susceptible to clindamycin but resistant to erythromycin prior to prescribing clindamycin due to the potential for inducible clindamycin resistance, particular in infections with a high organism load. Clinicians should also be aware that more resistant nosocomially-acquired MRSA infections can present in the outpatient setting many months after hospital discharge [Huang S, et al. *Clin Infect Dis* 2003;36:281]. A potential treatment option in the outpatient setting for these highly resistant infections is linezolid, the first drug in a new antibiotic class called the oxazolidinones [Moellering R, *Ann Intern Med* 2003;138:135]. Clinical experience with this new antibiotic is limited and adverse reactions can occur as outlined in Table 2, p 12.



## Management of Community-Associated Methicillin-Resistant *Staphylococcus aureus* Infections in the Outpatient Setting

**Table 1. Outpatient Evaluation of MRSA Skin and Soft Tissue Infections**

<b>Initial Assessment and Treatment</b>
<ul style="list-style-type: none"> <li>Assess risk factors for MRSA infection, e.g. recent hospitalization, IDU, MSM, outbreak setting.</li> <li>Evaluate skin lesion for cellulitis, crepitus, fluctuance, and sinus drainage.</li> <li>Drain/aspirate infection whenever possible and obtain cultures. Minor infections may resolve with incision and drainage alone.</li> </ul>
<b>Empiric Therapy</b>
<ul style="list-style-type: none"> <li>Treat with oral antibiotics for serious infections such as large or multiple furuncles, abscesses, deep-seated folliculitis, and ecthyma.</li> <li>No MRSA risk factors: Consider cephalexin, or amoxicillin/clavulanate, or erythromycin.</li> <li>In context of MRSA outbreak or presence of MRSA risk factors then treat with TMP-SMX ± rifampin, or clindamycin ± rifampin.*</li> <li>Treat with clindamycin rather than TMP-SMX if streptococcal infection is in differential.</li> <li>Treat with IV vancomycin for severe skin infections, such as marked cellulitis and for any evidence of invasive disease, e.g. sepsis.</li> <li>Use lower threshold for IV vancomycin for patients recently discharged from the hospital.</li> </ul>
<b>Targeted Antibiotic Therapy</b>
<ul style="list-style-type: none"> <li>If cultures and antibiotic sensitivities are available, target therapy accordingly.</li> <li>If susceptible, consider treatment with TMP-SMX ± rifampin or clindamycin ± rifampin.*</li> <li>Monitor pt.: persistent/recurrent disease may indicate nonadherence, new infection, or resistance.</li> <li>Highly resistant MRSA isolates and serious infections usually require IV vancomycin therapy.</li> </ul>
<b>Treatment Follow-Up</b>
<ul style="list-style-type: none"> <li>Re-evaluate throughout course of treatment; examine for recurrent lesions during follow-up visits.</li> <li>Provide patient education on prevention.</li> <li>Continue periodic follow-up as clinically warranted.</li> </ul>

\*Rifampin is not a treatment option due to drug interactions for most patients on antiretroviral therapy.

The duration of antibiotic therapy should be based on the severity of the infection and the clinical response. Adequately drained, uncomplicated skin and soft tissue CA-MRSA infections usually resolve with 10-14 days of antibiotics. Systemic infections, such as sepsis and osteomyelitis require intravenous antibiotics and a longer total duration of antibiotic therapy. Patients should be monitored closely, even after antibiotics have been discontinued, since recurrent infections at the same or different site commonly occur. Decolonization of the nares and other body sites, including the ears, navel, axillae, groin, and interdigital toe web spaces, by treating with topical mupirocin is of unproven benefit, but has been tried as an adjunct to oral antibiotics, particularly in an outbreak setting and in persons with recurrent infections, e.g. 3 or more infections within 6 months.

### Prevention

CA-MRSA infections represent a new potential health threat for persons with HIV infection regardless of their CD4+ T-cell count or viral load; therefore preventing these infections should be a priority for both patients and their providers. Reinforcing hand hygiene as a personal health concern is the most important prevention message for patients, since MRSA is primarily transmitted from person to person through direct contact by contaminated hands. Investigations of CA-MRSA outbreaks have also implicated the sharing of common objects, such as athletic equipment, towels, and personal items [MMWR 2003;52(05):88]. Patients already infected with CA-MRSA should be advised on methods for containing their infection and preventing self-inoculation. Patient-counseling messages for preventing CA-MRSA infections are outlined in Table 3.

### Summary

The emergence of CA-MRSA infections is an additional threat to the growing global public health crisis of antimicrobial

resistance. Efforts to control MRSA infections can no longer depend solely on surveillance, infection control efforts, and judicious antibiotic prescribing practices within the hospital setting. Proactive patient education, aggressive diagnostic efforts, and effective treatment for CA-MRSA infections by outpatient clinicians, will not only improve patient care, but also protect our communities and hospitals from an increasingly prevalent pathogen. ▲

**Table 3. How to Prevent "MRSA" Infections - Patient Information**

- Wash your hands thoroughly throughout the day whenever they are visibly dirty, after you use the bathroom, and before every meal.
- Maintain good personal hygiene by taking regular baths or showers.
- Do not share personal hygiene items with other including toiletries and towels.
- Clean off communal surfaces such as recreational equipment, sauna or steam room sitting areas before direct contact with your body; use a clean barrier such as a towel or shirt between your bare skin and these communal surfaces whenever feasible.
- Shower after participating in close-contact recreational activities, or attending public gyms, saunas, steam rooms, or bathhouses.
- Be aware of close personal contacts such as family members and sexual contacts who may have skin infections.
- Do not touch another person's wounds, infected skin, or soiled bandages with your bare hands.
- Seek your doctors advice for any boils or new sores that are red or inflamed.
- Do not scratch skin rashes; seek treatment from your doctor that can reduce itching.
- Be alert for any skin infections following hospital discharge.
- If you have a MRSA infection, tell your close contacts so they can avoid exposures, contain any drainage with a dressing, wash your hands after every contact with the wound so you do not spread the infection to other parts of your body, and follow your doctors orders so the infection can be cured.

*continued on page 12*



## Management of Community-Associated Methicillin-Resistant *Staphylococcus aureus* Infections in the Outpatient Setting

continued from page 11

Table 2. Outpatient Treatment Options for CA-MRSA Skin and Soft Tissue MRSA Infections\*

Drug	Oral Dose	Drug Interactions/Effects	Comments
<b>TMP-SMX</b>	1 DS tablet every 8-12 hrs.	<ul style="list-style-type: none"> <li>• Drug interactions: dapsone, anticoagulants, phenytoin, cyclosporine, diuretics, methotrexate</li> <li>• Adverse effects: rash, erythema multiforme, Stevens-Johnson syndrome hemolysis/G-6-PD deficiency, hepatitis, pancreatitis, bone marrow suppression</li> </ul>	<ul style="list-style-type: none"> <li>• Check for sulfa allergy</li> <li>• Do not use for empiric therapy if streptococcal infection is clinically suspected</li> <li>• Check drug interactions with rifampin, particularly antiretroviral medicines</li> </ul>
<b>+ or - Rifampin</b>	300 mg bid		
<b>Clindamycin</b>	150 mg-300 mg q 6 hrs.	<ul style="list-style-type: none"> <li>• Adverse effects: GI upset and risk of <i>C. difficile</i> pseudomembranous colitis</li> </ul>	<ul style="list-style-type: none"> <li>• Potential for inducible resistance that may be clinically relevant particularly with large organism load; if isolate resistant to erythromycin consult with microbiology laboratory to conduct "D" test to detect inducible resistance</li> <li>• Good bone penetration</li> <li>• Check drug interactions with rifampin, particularly antiretroviral medicines</li> </ul>
<b>+ or - Rifampin</b>	300 mg bid		
<b>Fluoroquinolone</b> Ciprofloxacin - or	500 mg q 12	<ul style="list-style-type: none"> <li>• Rare risk of Achilles tendon rupture</li> <li>• Absorption of quinolones is impaired when taken with antacids - avoid co-administration</li> </ul>	<ul style="list-style-type: none"> <li>• <b>Caution:</b> Efficacy of quinolones may be affected by the rapid development of resistance; addition of rifampin should be considered</li> <li>• Check drug interactions with rifampin, particularly antiretroviral medicines</li> </ul>
Levofloxacin - or	500 mg q day		
Gatifloxacin - or	400 mg q day		
Moxifloxacin - or	400 mg q day		
<b>+ Rifampin</b>	300 mg bid		
<b>Linezolid (Zyvox<sup>®</sup>)</b>	600 mg bid	<ul style="list-style-type: none"> <li>• Adverse effects: diarrhea, bone marrow suppression, nausea, headache; potential for peripheral neuropathy, optic neuritis, and serotonin syndrome when combined with SSRIs, e.g. paroxetine and citalopram, particularly with chronic usage.</li> </ul>	<ul style="list-style-type: none"> <li>• <b>Caution:</b> Efficacy and toxicity data are limited; reserve for highly resistant infections</li> <li>• Patients must avoid foods with large amounts of tyramine</li> <li>• Avoid in patients with hypertension</li> <li>• Avoid adrenergic and serotonergic agents, including decongestants</li> <li>• Expensive</li> </ul>

**\*Other Key Points:**

- Another potential treatment option is minocycline or doxycycline 100 mg q 12 hours; in vitro resistance to tetracycline may or may not indicate doxycycline resistance.
- Never treat with rifampin alone since resistance will develop rapidly. The benefit of adding rifampin as a second antibiotic to treat CA-MRSA infection is unknown.
- Intravenous therapy is recommended for serious CA-MRSA infections including, severe skin and soft tissue infections, sepsis, endocarditis, pneumonia, and osteomyelitis.

### THE HOPKINS HIV REPORT

The Johns Hopkins University AIDS Service  
*The Hopkins HIV Report* Distribution  
P.O. Box 651266  
Potomac Falls, VA 20165-1266

**ADDRESS SERVICE REQUESTED**

Non-Profit Org.  
U.S. Postage  
**PAID**  
Dulles, VA  
Permit No. 056